Total Synthesis of Fluorinated Analogues of Inositol and Inositol 1,4,5-Trisphosphate

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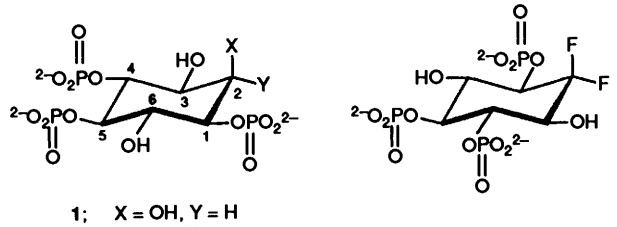
Syntheses of fluorinated analogues of inositol and inositol 1,4,5-trisphosphate are described. 1-Deoxy-1-fluoro-*scyllo*-inositol, 2-deoxy-2,2-difluoro-*myo*-inositol, DL-2-deoxy-2-fluoro-*scyllo*-inositol 1,4,5-trisphosphate and DL-2-deoxy-2,2-difluoro-*myo*-inositol 1,4,5-trisphosphate have been prepared. Preparation of the (−)-camphanate ester of DL-3,6-di-*O*-benzyl-2-deoxy-2,2-difluoro-4,5-*O*-isopropylidene-*myo*-inositol facilitated the chromatographic separation of diastereoisomers. The absolute configuration of the diastereoisomeric camphanate of the protected D-*myo*-inositol derivative was determined by single-crystal X-ray crystallography. The separated diastereoisomers, after removal of camphanate and isopropylidene moieties, were used to synthesize both the D- and the L-enantiomer of 2-deoxy-2,2-difluoro-*myo*-inositol 1,4,5-trisphosphate.

D-*myo*-inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] **1** is a second messenger which mediates the release of Ca^{2+} from intracellular stores[1,2] *via* a receptor which has been isolated,[3] cloned,[4] and sequenced[5] and which, when reconstituted, mediates Ca^{2+} release in response to Ins(1,4,5)P_3.[6] A major challenge is now the elucidation of the structural basis for interaction of Ins(1,4,5)P_3 both with its receptor and with the metabolic enzymes Ins(1,4,5)P_3 3-kinase and 5-phosphatase, and the rational chemical design of agonists, antagonists, and enzyme inhibitors. Recent progress in inositol phosphate chemistry[7,8] and the molecular recognition of inositol phosphates has been reviewed.[9]



1; X = OH, Y = H
2; X = Y = H
3; X = H, Y = F
D-**4a**; X = Y = F

L-**4b**

Structures of Ins(1,4,5)P_3 and analogues. Except for compound **4** only D-isomers are shown.

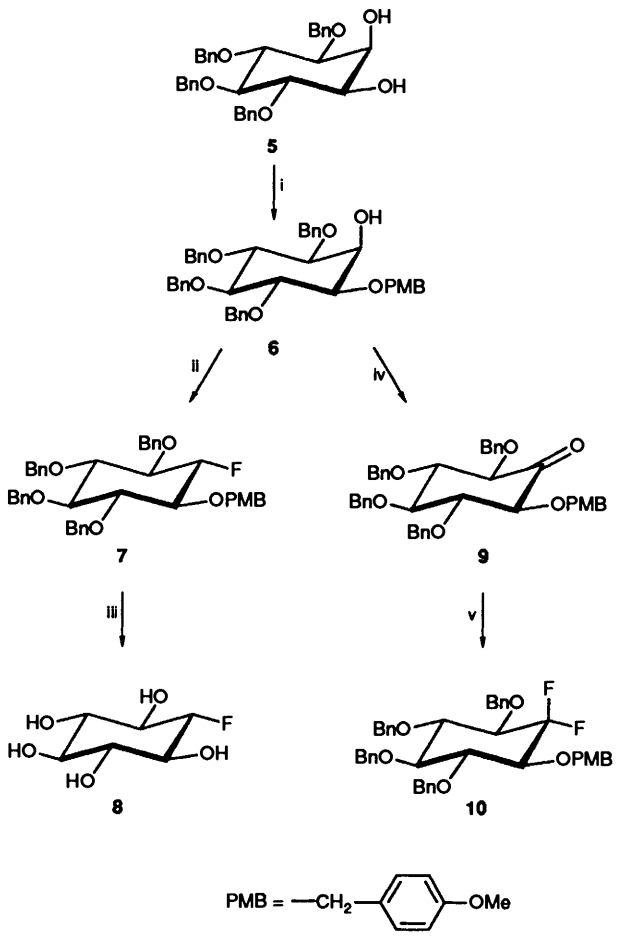
Several inositol ring-modified and phosphate-modified analogues have been synthesized[7,8] and some progress has been made to understand the role of the three phosphate and hydroxy groups of Ins(1,4,5)P_3 in receptor-binding specificity and stimulation. Isosteric replacement of a hydroxy group with fluorine[10] has led to fluorinated *myo*-inositol analogues[11–17] and derivatives,[18] and *myo*-inositol phosphate analogues[19–23] and others, including 2-deoxy-2-fluoro-1-phosphatidyl-*scyllo*-inositol.[24] D-3-Deoxy-3-fluoro-*myo*-inositol inhibits cell growth in NIH 3T3 cells[13] and 5-deoxy-5-fluoro-*myo*-inositol is taken up by L1210 cells and incorporated into cellular phospholipid by PtdIns synthase,[25] although 5-deoxy-5,5-difluoro-*myo*-inositol is a much poorer substrate.[15] Five reports of biological activity for non-fluorinated ring-modified analogues of Ins(1,4,5)P_3 **2**, including DL-2-deoxy-Ins(1,4,5)P_3, have appeared.[26–30] We recently reported the first biological evaluation of some fluorinated inositol phosphate analogues[22] and studied the interaction of the two synthetic analogues 2-deoxy-2-fluoro-*scyllo*-inositol 1,4,5-trisphosphate [2F-Ins(1,4,5)P_3] **3**† and 2-deoxy-2,2-difluoro-Ins(1,4,5)P_3 [2,2-F_2-Ins(1,4,5)P_3] **4** with the Ca^{2+}-releasing receptor of SH-SY5Y neuroblastoma cells and the metabolic enzymes Ins(1,4,5)P_3 5-phosphatase and 3-kinase. An unexpected result of these studies was that DL-2,2-F_2-Ins(1,4,5)P_3, although in other respects an excellent Ins(1,4,5)P_3 analogue, was apparently not a substrate for the 5-phosphatase, unlike 2-deoxy-Ins(1,4,5)P_3.[27] We suspected that this phenomenon might be caused by L-2-deoxy-2,2,-difluoro-*myo*-inositol trisphosphate acting as a potent 5-phosphatase inhibitor. To investigate this possibility further we have resolved compound **4** into its individual D- and L-enantiomers and we report here full synthetic methods for the synthesis of fluorinated inositol and inositol phosphate analogues.

Results and Discussion

(±)-1,4,5,6-Tetra-*O*-benzyl-*myo*-inositol **5** was prepared by modifications of the published method.[31] Thus, (±)-1,2-*O*-isopropylidene-*myo*-inositol[32] was benzylated using an excess of sodium hydride and benzyl bromide in dimethylformamide (DMF) in the usual way and the ketal from the resulting (±)-3,4,5,6-tetra-*O*-benzyl-1,2-*O*-isopropylidene-*myo*-inositol was removed by treatment with 80% aq. acetic acid at 100 °C for 15 min.

The dibutylstannylene derivative of diol **5** was prepared using dibutyltin oxide.[33] Regiospecific alkylation of the 1-position with *p*-methoxybenzyl chloride, followed by work-up afforded after purification, crystalline **6**. This compound was used in two ways. First, it was treated with (diethylamino)sulfur trifluoride (DAST), which inverted the 2-hydroxy group to yield the corresponding 2-deoxy-2-fluoro-*scyllo* derivative **7**. Com-

† Note that the nomenclature used in this paper for poly(phosphates) is designed to show the relationship of synthetic analogues to D-*myo*-inositol 1,4,5-trisphosphate. Alternative names are as follows: for **3** 1-deoxy-1-fluoro-*scyllo*-inositol 2,4,5-trisphosphate; and for **4**, 1-deoxy-1,1-difluoro-*scyllo*-inositol 2,4,5-trisphosphate or 2-deoxy-2,2-difluoro-*scyllo*-inositol 1,4,5-trisphosphate. To avoid confusion, unphosphorylated precursors for these compounds have been named in the same fashion. 'Inositol' refers to the *myo*-isomer unless specified.



Scheme 1 Synthesis of fluorinated inositol analogues. *Reagents and conditions:* i(a) Bu_2SnO (1.2 mol equiv.), toluene, reflux, 3 h; (b) CsF (2 mol equiv.), KI (1.5 mol equiv.), *p*-$MeOC_6H_4CH_2Cl$ (1.3 mol equiv.), DMF, room temp. 24 h; (c) aq. $NaHCO_3$; ii(a) DAST (3.6 mol equiv.), CH_2Cl_2, 0 °C, 2 h; (b) aq. $NaHCO_3$; iii(a) Na–liq. NH_3, −78 °C, 20 min; (b) H^+-Dowex, water; iv(a) Ac_2O (24 mol equiv.), DMSO, room temp., 24 h; (b) aq. $NaHCO_3$; v(a) DAST (12.4 mol equiv.), CH_2Cl_2, room temp., 12 h; (b) aq. $NaHCO_3$.

pound **7** was deblocked reductively by using sodium in liquid ammonia to yield 1-deoxy-1-fluoro-*scyllo*-inositol **8**.* Compound **6** was also converted into the corresponding 2-inosose **9** by oxidation with dimethyl sulfoxide (DMSO) and acetic anhydride. Conversion into the 2,2-difluoro derivative **10** was accomplished by using DAST (Scheme 1). 2-Deoxy-2,2-difluoro-*myo*-inositol **20** (Scheme 2) was not prepared *via* deblocking of the pentakis ether **10**, although this should be possible, but rather from the triol **19** (*vide infra*).

In order to synthesize fluorinated inositol trisphosphates **3** and **4** the following approaches were adopted: Isomerisation of the 1-*O*-allyl group of compound **11**[35] by using potassium *t*-butoxide gave the corresponding 1-*O*-[(*Z*)-propenyl] derivative **12**, which was fluorinated with inversion of configuration to give the protected 2-deoxy-2-fluoro-*scyllo*-inositol derivative **13**. Deblocking of compound **13** with acid afforded the triol **14**, which after phosphitylation with bis-(2-cyanoethyl)diisopropylaminophosphine, oxidation of the corresponding trisphosphite to the trisphosphate **15**, and complete deblocking with sodium in liquid ammonia, in a similar fashion to that described in our reported synthesis of Ins(1,4,5)P_3,[36] then gave racemic 2-deoxy-2-fluoro-*scyllo*-inositol 1,4,5-trisphosphate **3**, which was purified by ion-exchange chromatography on DEAE Sephadex and quantified using an adaptation of the Briggs phosphate assay.

Compound **11** was also oxidised with acetic anhydride–DMSO to the corresponding protected 2-inosose **16**,[35] which was fluorinated with DAST to the 2,2-difluoro derivative **17**. Isomerisation of the 1-*O*-allyl group of **17** by using Wilkinson's catalyst gave the 1-*O*-prop-1-enyl derivative **18** as a 2:9 mixture of *E*:*Z* isomers. Acidic hydrolysis generated the racemic triol **19ab**, which was then converted into 2-deoxy-2,2-difluoro-*myo*-inositol **20** by catalytic hydrogenation over Pd/C under pressure. Compound **19ab** was also phosphitylated to the corresponding trisphosphite, which was oxidised to the corresponding trisphosphate **21** and fully deblocked in sodium–liquid ammonia to afford, after purification by ion-exchange chromatography, racemic 2-deoxy-2,2-difluoro-*myo*-inositol 1,4,5-trisphosphate **4** (Scheme 2).

The optical isomers of compound **4** were prepared as follows: Racemic triol **19ab** was converted into the 4,5-isopropylidene ketal **22ab**, which was then treated with (*S*)-(−)-camphanyl chloride to afford the diastereoismeric 1-camphanates **23** and **24**. These camphanates were well separated on TLC (R_f-values 0.19, 0.29, respectively) and were conveniently separated by flash column chromatography on silica gel. The absolute configuration of diastereoisomer **23** was determined by single-crystal X-ray crystallography and this isomer was designated D-3,6-di-*O*-benzyl-1-*O*-[(*S*)-(−)-camphanyl]-2-deoxy-2,2-difluoro-4,5-*O*-isopropylidene-*myo*-inositol (Fig. 1). Both diastereomers were deblocked by successive treatment with sodium hydroxide to remove the camphanate, and acid to remove the ketal, to give the D- and L-enantiomers of triol **19**, D-**19a** and L-**19b**, respectively. Both isomers were phosphorylated and the fully protected trisphosphates were deblocked, as described for racemic material, to yield after purification and phosphate assay the pure D- and L-enantiomers of 2-deoxy-2,2-difluoro-*myo*-inositol 1,4,5-trisphosphate, D-**4a** and L-**4b**, respectively (Scheme 3).

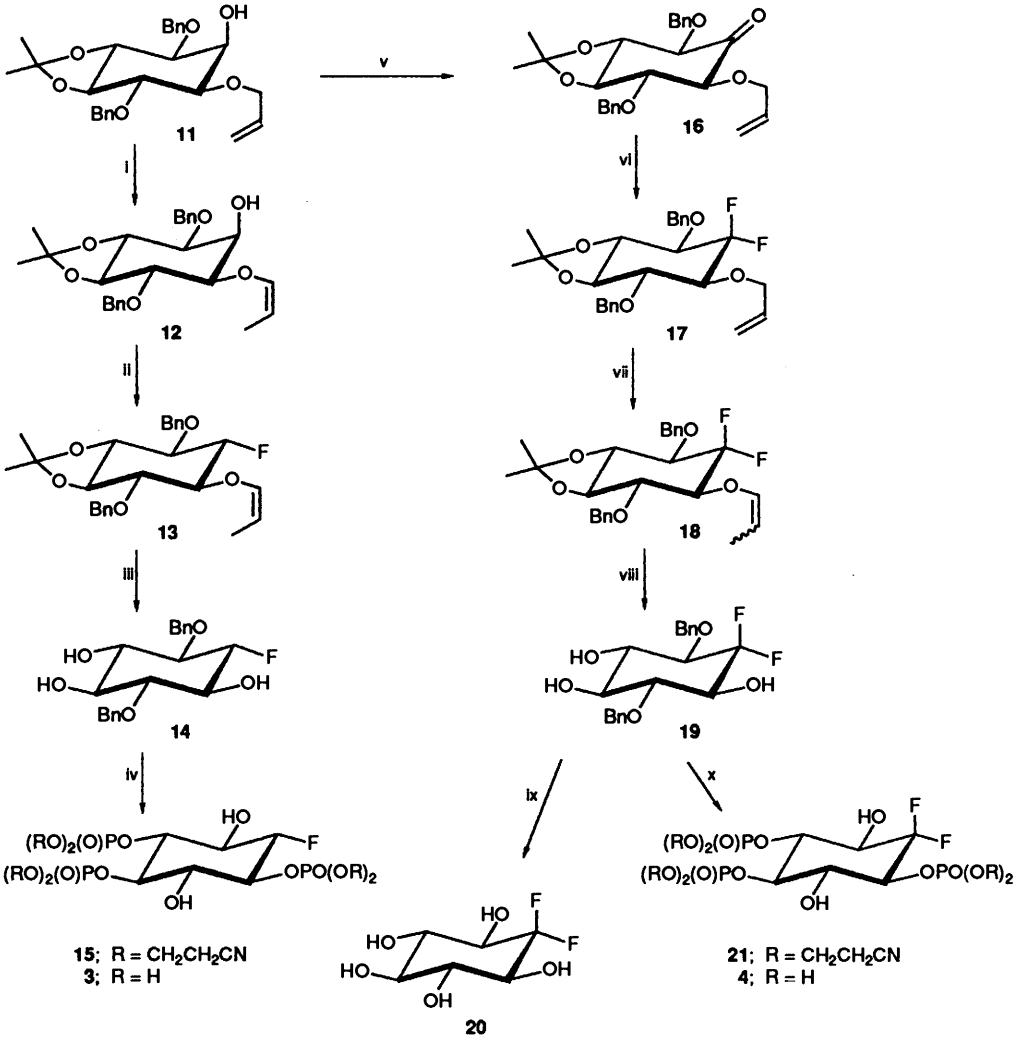
The interactions of compounds **3** and **4** with the Ins(1,4,5)P_3 receptor and the metabolic enzymes 3-kinase and 5-phosphatase have been published.[22] We have also reported our further studies on the interaction of D-**4a** and L-**4b** with these proteins. These studies have established D-**4a** as a potent Ca^{2+}-releasing agonist and L-**4b** as both a 5-phosphatase and 3-kinase inhibitor.[37]

Experimental

Materials and Methods.—The following abbreviations are used: PTSA, toluene-*p*-sulfonic acid; PMB, *p*-methoxybenzyl; Bn, benzyl; DABCO, diazabicyclo[2.2.2]octane; Wilkinson's catalyst, tris(triphenylphosphine)rhodium(I) chloride; H^+ Dowex, Dowex resin in hydrogen form; Ins(1,4,5)P_3, D-*myo*-inositol 1,4,5-trisphosphate; DEAE Sephadex is diethylaminoethylSephadex.

Light petroleum refers to the fraction boiling in the range 40–60 °C unless otherwise stated, ether refers to diethyl ether, and evaporation refers to removal of solvent on a rotary evaporator under reduced pressure. DMSO and dichloromethane were dried over calcium hydride and distilled. Acetone was dried over calcium sulfate and distilled. Pyridine was dried over potassium hydroxide and distilled. 1,4-Dioxane was dried over sodium metal and distilled. DAST was obtained from Aldrich Chemical Co. Ltd, and (*S*)-(−)-camphanyl chloride was from Fluka. TLC was performed on pre-coated plates (Merck Silica 60F). Flash chromatography refers to the method of Still *et al.*[38] IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer and were measured in a dichloromethane solution. Mass spectra were recorded either using a Micromass

* After this paper had been submitted, a paper relating to the synthesis of fluorinated inositol analogues appeared: see ref. 34.



Scheme 2 Synthesis of fluorinated inositol phosphate analogues. *Reagents and conditions:* i(a) KOBu^t (3 mol equiv.), DMSO, 50 °C, 3 h; (b) water; ii(a) DAST (3 mol equiv.), CH_2Cl_2, 0 °C, 1 h; (b) aq. $NaHCO_3$; iii(a) 1 mol dm^{-3} HCl–MeOH (1:5), reflux, 30 min; (b) excess of solid $NaHCO_3$; iv(a) $(NCCH_2CH_2O)_2PNPR^i_2$ (10 mol equiv.), tetrazole (13 mol equiv.), CH_2Cl_2, room temp., 1 h; (b) excess of 70% aq. Bu^{t}OOH, −78 °C, 1 h; (c) Na–liq. NH_3, −78 °C, 15 min; (d) H^+-Dowex, water; v Ac_2O (21 mol equiv.), DMSO, room temp., 16 h; (b) aq. $NaHCO_3$; vi(a) DAST (4 mol equiv.), CH_2Cl_2, room temp., 5 h; (b) aq. $NaHCO_3$; vii(a) DABCO (0.2 mol equiv.), $(Ph_3P)_3RhCl$ (0.08 mol equiv.), EtOH–water (9:1), reflux, 2 h; (b) water; viii(a) 1 mol dm^{-3} HCl–MeOH (1:5), reflux, 30 min; (b) excess of solid $NaHCO_3$; ix 10% Pd/C, H_2, EtOH–HOAc (9:1), 50 psi, 3 days; x(a) $(NCCH_2CH_2O)PNPr^i_2$ (11.5 mol equiv.), tetrazole (13 mol equiv.), CH_2Cl_2, room temp., 1 h; (b) excess of 70% aq. Bu^{t}OOH, −78 °C, 1 h; (c) Na–liq. NH_3, −78 °C, 15 min; (d) H^+-Dowex, water.

16B instrument or by the SERC mass spectrometry centre, Swansea. Rotations were measured in either a chloroform, acetone, or deuteriated water solution in a Perkin-Elmer 141 polarimeter.

Synthetic phosphates were assayed by adaptations of the Briggs phosphate test[39] as follows. For the qualitative test, each sample to be assayed was pipetted into a test tube and drops of conc. sulfuric acid were added to each tube, which was then heated in an oven at 200 °C for 45 min. The tubes were allowed to cool and water (250 mm^3) was added to each to dissolve the residue. An aliquot (500 mm^3) of a solution of ammonium molybdate (2.5 g) in water (20 cm^3) and conc. sulfuric acid (8 cm^3) was added, followed by an aliquot (250 mm^3) of a solution of hydroquinone (0.1 g) in water (20 cm^3) and one drop of conc. sulfuric acid, then finally an aliquot (250 mm^3) of a solution of sodium sulfite (4 g) in water (20 cm^3) was added. The mixture was heated to boiling for 10 s. A blue colour indicated the presence of inorganic phosphate.

For the quantitative assay the mixtures as treated above were transferred to volumetric flasks and made up to 10 cm^3. The UV absorvance at 340 nm was recorded using 3 cm^3 quartz cells. Concentration was calculated from a standard curve which was drawn from UV absorbance values of known concentrations of KH_2PO_4 treated as above and measured at 340 nm.

^1H and ^{13}C NMR spectra were recorded on a Bruker AM300 NMR spectrometer. Chemical shifts were measured in ppm relative to tetramethylsilane (TMS). ^{31}P and ^{19}F NMR spectra were recorded on either Bruker AM300 or JEOL FX90 NMR spectrometers. ^{31}P NMR chemical shifts were measured in ppm relative to external 85% H_3PO_4. ^{19}F NMR chemical shifts were measured in ppm relative to trichlorofluoromethane. *J*-Values are given in Hz. M.p.s (uncorrected) were determined using a Kofler micro heating stage. Microanalysis data were obtained from either Butterworths Laboratories Ltd, Middlesex or CHN Analysis Ltd, Leicester.

Compound **23** was prepared for X-ray crystallography as follows: crystals of compound **23** were recrystallised twice from an ether–hexane mixture. The crystals were collected, dissolved in redistilled dichloromethane, and the solution was filtered through a fine sinter. The solvent was removed by evaporation in a stream of nitrogen and the crystals were dissolved in

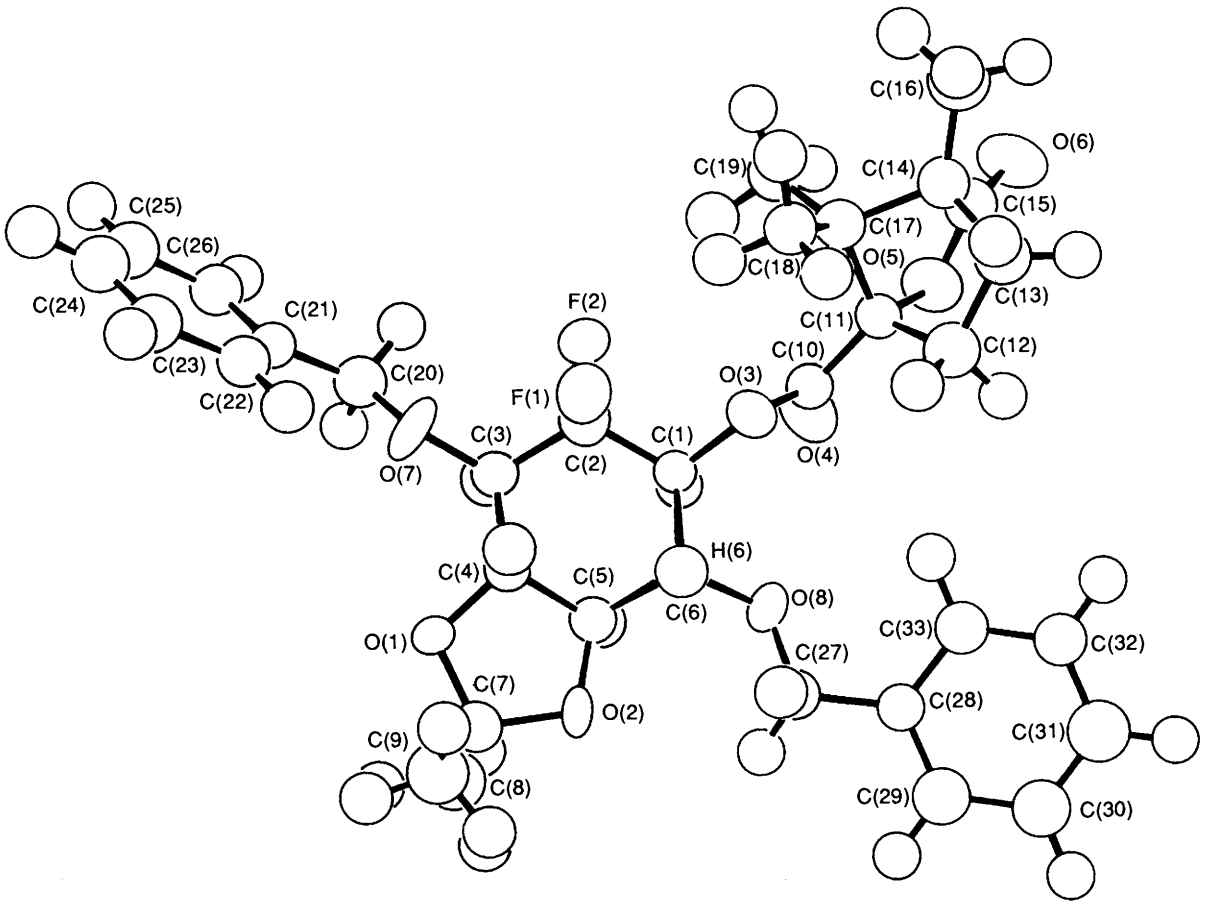


Fig. 1 Absolute configuration of 3,6-di-*O*-benzyl-1-*O*-[(*S*)-(−)-camphanyl]-2-deoxy-2,2-difluoro-4,5-*O*-isopropylidene-D-*myo*-inositol **23** determined by X-ray analysis

prefiltered, redistilled ether. The solvent was allowed to evaporate slowly to yield a suitable crystal for X-ray analysis.

The unit-cell parameters were determined by least-squares refinement of ω measurements for different layers.[40] The intensities of 2589 unique reflections with $2\theta < 50°$ and ($\pm h$, $+k$, $+l$) were measured on a Stoe STADI-2 Weissenberg diffractometer, with graphite-monochromated Mo-Kα radiation using an ω-scan technique. The data were corrected for Lorentz and polarisation effects to yield 1142 reflections with $I > 3\sigma(I)$. The structure was solved using the TREF option of SHELXS86.[41] All subsequent calculations were carried out using the computer program SHELX76.[42]

Hydrogen atoms were not located on the difference Fourier map, and all hydrogen atoms were included in calculated positions (C–H 1.08 Å), with a common fixed isotropic thermal parameter of 0.05 Å. The carbon atoms were refined with isotropic thermal parameters, and the oxygen and fluorine atoms were refined with anisotropic thermal parameters.

Final cycles of refinement employed a weighting parameter $g(0.0008)$ $\{w = 1/[\sigma^2(F) + g(F)^2]\}$ and gave the final residual indices $R\{ = \Sigma|(|F_o| - |F_c|)|/\Sigma|F_o|\}$ 0.069 and $R_w\{ = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}}\}$ 0.068. The final difference Fourier was featureless and an analysis of the weighting scheme over $|F_o|$ and $\sin\theta/\lambda$ was satisfactory.

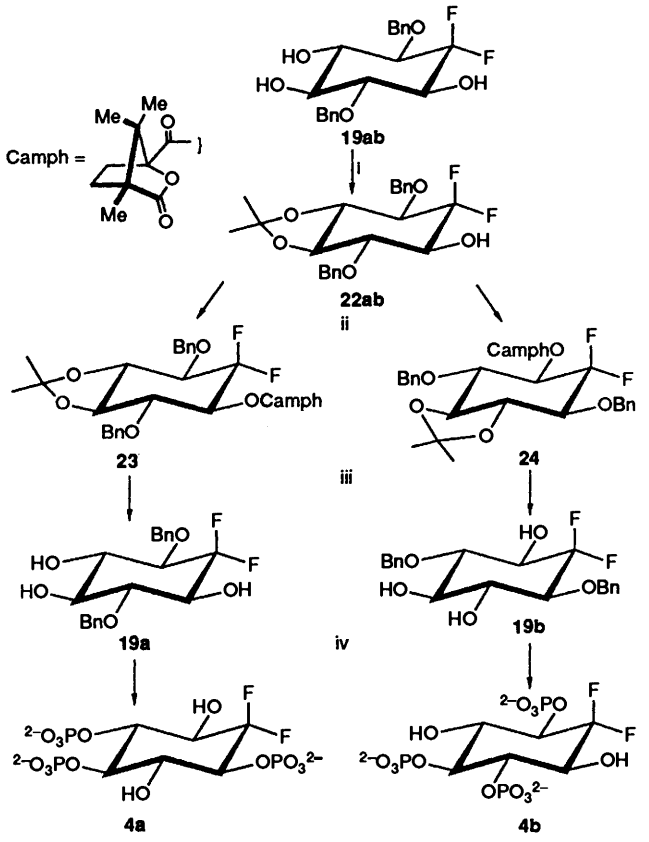
Single-crystal X-ray analysis was performed as follows.

* Atomic co-ordinates, thermal parameters, bond lengths, bond angles and non-bonded contacts have been desposited at the Cambridge Crystallographic Data Centre (for details, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1).

Crystal data. $C_{33}H_{38}O_8F_2$, $M = 600.65$, Monoclinic, space group = $P2_1$, $a = 8.602(10)$, $b = 9.090(3)$, $c = 19.650(23)$ Å, $\beta = 95.24(5)°$, $V = 1530(3)$ Å^3, $Z = 2$, $\mu = 0.62$ cm^{-1}, λ(Mo-Kα) = 0.7107 Å, $F(000) = 636.0$, $D_c = 1.30$ g cm^{-3}.

The geometry of the molecule is shown in Fig. 1.*

(±)-3,4,5,6-*Tetra*-O-*benzyl*-1-O-(p-*methoxybenzyl*)-*myo*-*inositol* **6**.—The tetra-*O*-benzyl-*myo*-inositol derivative **5**[31] (6.48 g, 12.8 mmol) and dibutyltin oxide (3.83 g, 15.4 mmol) were heated under reflux in toluene (150 cm^3) using a Dean–Stark apparatus for 3 h. The solution was allowed to cool and the solvent was removed under reduced pressure. CsF (3.89 g, 25.6 mmol) was added to the crude product and the mixture was dried over phosphorus pentaoxide for 1 h. Pre-dried potassium iodide (3.12 g, 19.2 mmol) and dry DMF (150 cm^3) were added to the reaction mixture. The apparatus was flushed out with nitrogen, and *p*-methoxybenzyl chloride (2.27 cm^3, 16.64 mmol) was added *via* a syringe. The reaction mixture was stirred under nitrogen at room temperature overnight. TLC [ethyl acetate–light petroleum (2:3)] showed a major product (R_f 0.6) and a small amount of unchanged starting material (R_f 0.34). The DMF was evaporated under reduced pressure and the residue was taken up in ether, and washed successively with water, aq. sodium hydrogencarbonate (10%), and again with water. The white precipitate formed was removed by filtration through Celite, and the ethereal layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel [ethyl acetate–light petroleum (2:3)] to give pure *title compound* **6** (6.8 g, 82%), m.p. 126–127 °C (from ethyl acetate–hexane) (Found: C, 76.25; H, 6.9. $C_{42}H_{44}O_7$ requires C, 76.34; H, 6.71%); *m/z* 678 [(M + NH_4)$^+$,



Scheme 3 Resolution of triol 19 *via* the diastereoisomeric camphanates. *Reagents and conditions:* i(a) $(MeO)_2CMe$ (40 mol equiv.), PTSA–Me_2CO, room temp., 2 h; (b) Et_3N, solid $NaHCO_3$; ii(a) (*S*)-(−)-camphanyl chloride (2 mol equiv.), C_5H_5N, room temp., 12 h; (b) water; iii(a) NaOH, MeOH, reflux, 1 h; (b) 1 mol dm^{-3} HCl–MeOH (1:5), reflux, 30 min; (c) excess of solid $NaHCO_3$; iv(a) $(NCCH_2CH_2O)_2PNPr^i_2$ (6 mol equiv.), tetrazole (10 mol equiv.), CH_2Cl_2, room temp., 1 h; (b) excess of 70% aq. Bu^tOOH, −78 °C, 1 h; (c) Na–liq. NH_3, −78 °C, 15 min; (d) H^+-Dowex, water.

22%], 569 [$(M - Bn)^+$, 10], 539 [$(M - PMB)^+$, 100] 121 (PMB^+, 100) and 91 (Bn^+, 100); ν_{max}/cm^{-1} 3585 (OH); $\delta_H(CDCl_3$; 300 MHz) 2.52 (1 H, br s, exch. D_2O, 2-OH), 3.36 [2 H, 2 × dd (overlapping), *J* 9 and 2.5, 1- and 3-H), 3.62 (1 H, t, *J* 9, CH), 3.77 (3 H, s, OMe) 3.98 (1 H, t, *J* 9, CH) 4.00 (1 H, t, *J* 9, CH), 4.18 (1 H, t, *J* 2.5, 2-H), 4.60–4.95 (10 H, m, CH_2Ar), 6.84 (2 H, d, *J* 9, PMBArH) and 7.20–7.40 (22 H, m, 4 × CH_2Ph and PMBArH); $\delta_C(CDCl_3$; 75 MHz) 55.2 (q), 67.48 (d), 72.31 (t), 72.64 (t), 75.85 (t), 79.43 (d), 79.73 (d), 81.16 (d), 83.14 (d), 113.8 (d), 127.46 (d), 127.78 (d), 127.9 (d), 128.25 (d), 128.37 (d), 129.45 (d), 129.96 (d), 137.91 (d), 138.63 (s), 138.7 (s), 138.74 (s) and 159.27 (s).

(±)-3,4,5,6-*Tetra*-O-*benzyl*-2-*deoxy*-2-*fluoro*-1-O-(p-*methoxybenzyl*)-scyllo-*inositol* **7**.—A solution of compound **6** (400 mg, 0.61 mmol) in dry dichloromethane (2 cm^3) was added dropwise to a solution of DAST (300 mm^3, 2.27 mmol) in dry dichloromethane (1 cm^3) at 0 °C under nitrogen. The reaction mixture was kept at 0 °C for 2 h and then allowed to warm to room temperature. After 1 h the reaction was quenched by the addition of saturated aq. sodium hydrogencarbonate. The dichloromethane layer was washed successively with saturated aq. sodium hydrogencarbonate (2 × cm^3) and brine (2 × 5 cm^3), dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography [ethyl acetate–light petroleum (1:4)] to give compound **7** (380 mg, 94%); m.p. 72–73 °C (from hexane) [Found: $(M + NH_4)^+$, 680.3387. $C_{42}H_{47}FNO_6$ requires $(M + NH_4)^+$, 680.3387]; *m/z* 680 $(M + NH_4)^+$, 541 $(M - PMB)^+$ and 121 (PMB^+, 100%); $\delta_H(CDCl_3$; 300 MHz) 3.56 (3 H, m, 3 × CH), 3.65 [2 H, 2 × dt (overlapping), *J* 12.8 and 9, 1- and 3-H), 3.76 (3 H, s, OMe), 4.55 (1 H, dt, *J* 51.3 and 9, 2-H), 4.67–4.91 (10 H, m, 5 × CH_2Ar), 6.83 (2 H, d, *J* 9, PMBArH) and 7.15–7.39 (22 H, m, 4 × CH_2Ph, and PMBArH); $\delta_C(CDCl_3$; 75 MHz) 55.18 (q), 75.05 (t), 75.36 (t), 75.90 (t), 80.52 and 80.85 (dd, C-1 or -3), 80.74 and 81.07 (dd, C-1 or -3), 81.22 (d), 81.39 (d), 82.38 (d), 95.23 and 97.66 (dd, C-2), 113.76 (d), 127.61 (d), 127.73 (d), 127.79 (d), 128.01 (d), 128.31 (d), 129.67 (d), 130.28 (s), 138.11 (s), 138.28 (s), 138.36 (s) and 159.28 (s); $\delta_F(CDCl_3$; 282 MHz) −193.824 (1 F, dt, *J* 51.3 and 12.8, 2-F^{eq}).

1-*Deoxy*-1-*fluoro*-scyllo-*inositol* **8**.—Ammonia was condensed into a 3-neck flask at −78 °C and an excess of sodium metal was added. The dry liquid ammonia (40 cm^3) was distilled into a second 3-neck flask and kept at −78 °C. Sodium was added until the solution remained blue. Compound **7** (100 mg, 0.15 mmol) was added as a solution in dry 1,4-dioxane (3 cm^3). The reaction mixture was stirred for 20 min and then quenched by the addition of ethanol. The ammonia was evaporated off in a stream of nitrogen and the crude product was taken up in water. The aq. solution was treated with H^+ Dowex until it was slightly acidic (universal indicator paper), the Dowex was removed by filtration and washed well with water, and the filtrate was made basic with triethylamine and evaporated to dryness. Crude title compound **8** (13 mg, 47%) was purified by recrystallization from methanol, m.p. 250–253 °C (lit.,[24] 250–253 °C); [Found: $(M + NH_4)^+$, 200.0934. Calc. for $C_6H_{15}FNO_5$: $(M + NH_4)^+$, 200.0934]; $\delta_H(D_2O$; 300 MHz) 3.40 (3 H, m, 3 × CH), 3.70 (2 H, m, 2 × CH) and 4.31 (1 H, dt, *J* 50.4 and 9, CHF); $\delta_F(D_2O$; 282 MHz) −197.084 (1 F, dt, *J* 50.4 and 12.6, CF^{eq}).

(±)-3,4,5,6-*Tetra*-O-*benzyl*-1-O-(p-*methoxybenzyl*)-myo-2-*inosose* **9**.—A solution of compound **6** (2.27 g, 4.27 mmol) in dry DMSO (2.5 cm^3) was added dropwise to a stirred solution of acetic anhydride (10 cm^3, 98 mmol) in dry DMSO (15 cm^3) under nitrogen at room temperature and left overnight. The reaction mixture was then added dropwise to stirred, aq. sodium hydrogencarbonate (50 g in 250 cm^3) during 1 h and then left for a further 2 h. The precipitated product was filtered off and washed well with water to give the *inosose* **9** (2.4 g, 86%), m.p. 136–137 °C (from ethyl acetate–hexane) (Found: C, 76.6; H, 6.2. $C_{42}H_{42}O_7$ requires C, 76.60; H, 6.38%) [Found: $(M + NH_4)^+$, 676.3274. $C_{42}H_{46}NO_7$ requires $(M + NH_4)^+$, 676.3274]; *m/z* (FAB, −ve) 657 [$(M - H)^+$, 26%], 537 [$(M - PMB)^+$, 35], 121 (PMB^+, 100) and 91 (Bn^+, 100); ν_{max}/cm^{-1} 1740 (C=O); $\delta_H(CD_2Cl_2$; 300 MHz) 3.56 (1 H, t, *J* 9, CH), 3.58 (1 H, t, *J* 9, CH), 3.77 (3 H, s, OMe), 3.85 (1 H, t, *J* 9, CH), 4.14 (1 H, d, *J* 9, 1- or 3-H), 4.17 (1 H, d, *J* 9, 3- or 1-H), 4.46 (1 H, d, *J* 10.5, CHH in PMB), 4.53 (1 H, d, *J* 10.5, CHH in PMB), 4.70–4.95 (8 H, m, 4 × CH_2Ph), 6.84 (2 H, d, *J* 9, PMBArH) and 7.20–7.45 (22 H, m, 4 × CH_2Ph, and PMB ArH); $\delta_C(CD_2Cl_2$; 75 MHz) 55.8 (q), 73.25 (t), 73.56 (t), 76.01 (t), 76.06 (t), 76.17 (t), 81.77 (d), 82.43 (d), 83.94 (d), 84.26 (d), 114.07 (d), 127.88 (d), 127.94 (d), 123.19 (d), 128.36 (d), 128.4 (d), 128.56 (d), 128.70 (d), 130.04 (d), 130.14 (d), 138.05 (s), 138.78 (s), 138.82 (s), 138.90 (s), 159.87 (s) and 202.62 (s).

(±)-3,4,5,6-*Tetra*-O-*benzyl*-2-*deoxy*-2,2-*difluoro*-1-O-(p-*methoxybenzyl*)-myo-*inositol* **10**.—A solution of ketone **9** (319 mg, 0.49 mmol) in dry dichloromethane (4 cm^3) was added dropwise to a solution of DAST (800 mm^3, 6.06 mmol) in dry dichloromethane (2 cm^3) at 0 °C under nitrogen. After addition was complete the reaction mixture was allowed to warm to room temperature and was left overnight. TLC [ethyl acetate–light petroleum (1:5)] showed a major product (R_f 0.32) and a

trace of starting material (R_f 0.23). The reaction was quenched by the addition of saturated aq. sodium hydrogencarbonate and the dichloromethane layer was washed with aq. sodium hydrogencarbonate solution (2 × 10 cm^3) and brine (2 × 10 cm^3), dried (Na_2SO_4), and evaporated to give crude product, which was purified by flash chromatography on silica gel [ethyl acetate–light petroleum (1:5)] to give *compound* **10** (245 mg, 75%), m.p. 118.5–119 °C (from hexane) (Found: C, 74.5; H, 6.1. $C_{42}H_{42}F_2O_6$ requires C, 74.12; H, 6.17%) [Found: $(M + NH_4)^+$, 698.3293. $C_{42}H_{46}F_2NO_6$ requires $(M + NH_4)^+$, 698.3293]; *m/z* (FAB; −ve) 679 $(M - H)^+$, 589 $[(M - Bn)^+$, 30%], 559 $[(M - PMB)^+$, 47], 211 (33), 181 (36), 121 (PMB^+, 100) and 91 (Bn^+, 100); $\delta_H(CDCl_3$; 300 MHz) 3.57 [2 H, 2 × dd (overlapping), *J* 17.6 and 9, 1- and 3-H], 3.67 (3 H, m, 3 × CH), 3.77 (3 H, s, OMe), 4.65–4.96 (10 H, m, 5 × CH_2Ar), 6.82 (2 H, d, *J* 9, PMBArH) and 7.17–7.45 (22 H, m, 4 × CH_2Ph, PMBArH); $\delta_C(CDCl_3$; 75 MHz) 55.19 (q), 75.47 (t), 75.82 (t), 76.03 (t), 76.11 (t), 76.15 (t), 78.98, 79.23 and 79.39 (dt, C-1 or -3), 79.47, 79.64 and 79.88 (dt, C-3 or -1), 80.72 (d), 80.84 (d), 82.09 (d), 113.78 (d), 117.10, 120.33 and 123.67 (t, C-2), 127.64 (d), 127.75 (d), 127.81 (d), 127.85 (d), 127.90 (d), 128.11 (d), 128.32 (d), 129.60 (s), 129.86 (d), 137.46 (s), 138.12 (s), 138.23 (s) and 159.43 (s); $\delta_F(CDCl_3$; 282 MHz) −113.82 (1 F, br d, *J* 250, 2-F^{eq}) and −127.49 (1 F, dt, *J* 250 and 17.6, 2-F^{ax}).

(±)-3,6-*Di*-O-*benzyl*-4,5-O-*isopropylidene*-1-O-[(Z)-*prop*-1-*enyl*]-myo-*inositol* **12**.—Compound **11**[35] (0.5 g, 1.14 mmol), dry DMSO (15 cm^3) and potassium *t*-butoxide (0.38 g, 3.34 mmol) were stirred at 50 °C under nitrogen for 3 h after which time TLC ether–light petroleum (1:1)] showed complete conversion of starting material (R_f 0.36) into a single product (R_f 0.44). The cooled reaction mixture was diluted with water (~20 cm^3) and the product was extracted into ether. The ethereal solution was dried ($MgSO_4$) and evaporated to dryness. The crude material was purified by flash chromatography on silica gel [ether–light petroleum (2:3)] to give pure *title compound* (0.5 g, 100%), m.p. 107–108 °C [from light petroleum (60–80 °C)] (Found: C, 71.0; H, 7.4. $C_{26}H_{32}O_6$ requires C, 70.89; H, 7.32%); *m/z* 440 (M^+, 14%), 349 (99), 181 (81), 127 (67), 107 (OBn^+, 69) and 91 (Bn^+, 100); $\delta_H(CDCl_3$; 300 MHz) 1.46 and 1.47 (6 H, 2 × s, CMe_2), 1.6 (3 H, dd, *J* 6.75 and 1.5, OCH=CH*Me*), 2.59 (1 H, d, *J* 1.5, 2-OH), 3.39 (1 H, t, *J* 9.75, CH), 3.58 (2 H, m, 1- and 3-H), 4.00 (1 H, dd, *J* 10.5 and 9.75, CH), 4.12 (1 H, t, *J* 9.75, CH), 4.25 (1 H, dt, *J* 1.5 and 4.5, 2-H), 4.46 (1 H, dq, *J* 6 and 6.75, OCH=C*H*Me), 4.75 (4 H, m, 2 × CH_2Ph), 6.05 (1 H, dq, *J* 6 and 1.5, OCH=CHMe), 7.30 (10 H, m, 2 × CH_2Ph); $\delta_C(CDCl_3$; 75 MHz) 9.3 (q), 26.9 (q), 27.0 (q), 70.46 (d), 71.59 (t), 73.23 (t), 75.47 (d), 77.13 (d), 79.06 (d), 83.43 (d), 102.18 (q), 111.88 (s), 127.42 (d), 127.74 (d), 127.89 (d), 128.16 (d), 128.39 (d), 137.80 (s), 138.43 (s) and 145.23 (d).

(±)-3,6-*Di*-O-*benzyl*-2-*deoxy*-2-*fluoro*-4,5-O-*isopropylidene*-1-O-[(Z)-*prop*-1-*enyl*]-scyllo-*inositol* **13**.—A solution of compound **12** (450 mg, 1.02 mmol) in dry dichloromethane (3 cm^3) was added *via* a dropping funnel to a stirred solution of DAST (400 mm^3, 3.03 mmol) in dry dichloromethane (2 cm^3) at 0 °C under nitrogen. The reaction mixture was kept at 0 °C for 1 h then allowed to warm to room temperature. TLC [ether–light petroleum (2:3)] showed conversion from starting material (R_f 0.35) to a major product (R_f 0.59). The reaction was quenched by addition of saturated aq. sodium hydrogen carbonate. The dichloromethane layer was washed successively with aq. sodium hydrogencarbonate (3 × 10 cm^3) and brine (2 × 10 cm^3), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography [ether–light petroleum (1:4)] to give compound **13** (301 mg, 68%), m.p. 204–205 °C [from ethyl acetate–light petroleum (60–80 °C)]; ν_{max}/cm^{-1} 1664 (CH=CHMe); *m/z* 442 (M^+, 7%), 351 (7), 278 (27), 220 (27), 203 (18), 107 (OBn^+, 100) and 91 (Bn^+, 100); $\delta_H(CDCl_3$; 300 MHz) 1.46 (6 H, s, CMe_2), 1.61 (3 H, dd, *J* 6.25 and 1.5, OCH=CH*Me*), 3.55 [2 H, 2 × t (overlapping), *J* 9, 2 × CH], 3.66 (1 H, t, *J* 9, CH), 4.42 (1 H, dq, *J* 6.0 and 6.25, OCH=C*H*Me), 4.58 (4 H, m, 2 × CH_2Ph), 6.11 (1 H, dq, *J* 6.0 and 1.5, OC*H*=CHMe) and 7.34 (10 H, m, 2 × CH_2Ph); $\delta_F(CDCl_3$; 282 MHz) −199.2 (1 F, ddd, *J* 49.5, 16.4 and 12.71, 2-F^{eq}); $\delta_C(CDCl_3$; 75 MHz) 9.21 (q), 26.92 (q), 72.71 (t), 73.29 (t), 76.83 (d), 76.99 and 77.09 (dd, C-1 or -3), 77.27 (d), 78.34 (d), 84.55 and 84.81 (dd, C-3 or -1), 95.35 and 97.82 (dd, C-2), 100.76 (d), 112.93 (s), 127.55 (d), 127.59 (d), 127.70 (d), 127.81 (d), 128.20 (d), 128.26 (d), 137.90 (s), 138.00 (s) and 146.46 (s).

(±)-3,6-*Di*-O-*benzyl*-2-*deoxy*-2-*fluoro*-scyllo-*inositol* **14**.—Compound **13** (400 mg, 0.9 mmol) was heated under reflux for 30 min in 1 mol dm^{-3} hydrochloric acid–methanol (1:5) (30 cm^3). An excess of sodium hydrogencarbonate was added to the cooled reaction mixture and the solvents were evaporated. The product was extracted from the residue with ethyl acetate and recrystallised from ethanol to give *compound* **14** (290 mg, 89%); m.p. 220–221 °C (from EtOH) (Found: C, 66.4; H, 6.4. $C_{20}H_{23}FO_5$ requires C, 66.28; H, 6.40%); *m/z* 380 $(M + NH_4)^+$, 271 $[(M - Bn)^+$, 10%], 107 (OBn^+, 20) and 91 (Bn^+, 100); $\delta_H([^2H_6]$DMSO; 300 MHz) 3.125 (1 H, t, *J* 9, CH), 3.30 (3 H, m, 3 × CH), 3.45 (1 H, m, CH), 4.24 (1 H, dt, *J* 51.75 and 9, 2-H), 4.75 (4 H, m, 2 × CH_2Ph), 5.07 (1 H, d, *J* 4.5, OH), 5.21 (1 H, d, *J* 4.5, OH), 5.46 (1 H, d, *J* 6, OH) and 7.32 (10 H, m, 2 × CH_2Ph); $\delta_F(CDCl_3$; 282 MHz) −200.76 (1 F, dt, *J* 51.75 and 11.2, 2-F^{eq}); $\delta_C([^2H_6]$DMSO; 75 MHz) 75.58 and 75.81 (dd, C-1 or -3), 76.85 and 77.01 (dd, C-4 or -6), 77.38 (t), 77.55 (d, C-5), 77.74 (t), 84.36 and 84.57 (dd, C-3 or -1), 85.54 and 85.70 (dd, C-6 or -4), 98.12 and 100.49 (dd, C-2), 130.95 (d), 131.11 (d), 131.37 (d), 131.46 (d), 131.62 (d), 131.80 (d), 131.92 (d), 143.05 (s) and 143.42 (s).

(±)-2-*Deoxy*-2-*fluoro*-scyllo-*inositol* 1,4,5-*Trisphosphate* **3**.—A mixture of triol **14** (82.8 mg, 228.7 μmol), tetrazole (214.6 mg, 3.06 mmol), and bis-(2-cyanoethyl)-*N*,*N*-diisopropylamino)-phosphine (645.7 mg, 2.38 mmol) was stirred at room temperature in dry dichloromethane (2 cm^3) for 1 h, after which time ^{31}P NMR spectroscopy showed the appearance of a signal at δ_P 141.8.

The phosphite was oxidised at −78 °C by addition of *t*-butyl hydroperoxide [1 cm^3 (70% soln. in water)]. The reaction mixture was allowed to warm to room temperature. ^{31}P NMR spectroscopy showed complete conversion of the trisphosphite (δ_P 141) into the phosphate triester **15** (δ_P −2.2, −2.6, −2.9). The reaction mixture was evaporated to dryness under reduced pressure. The crude product was partially purified by column chromatography on silica gel [dichloromethane–methanol (20:1)] to give the tris-triester (249.1 mg), which was not further characterised.

Ammonia was condensed into a 3-neck flask at −78 °C and an excess of sodium was added. The dry liquid ammonia (40 cm^3) was distilled into a second 3-neck flask and kept at −78 °C. Sodium was added until the solution remained blue. The phosphate triester (100 μmol) was added as a solution in dry 1,4-dioxane (5 cm^3). The reaction mixture was stirred for 15 min and then quenched by the addition of ethanol. The ammonia was evaporated off in a stream of nitrogen and the crude product was taken up in water. The aq. solution was treated with H^+-Dowex until the solution became slightly acidic (universal indicator paper), and the Dowex was removed by filtration and washed well with water. The filtrate was made basic by the addition of triethylamine and evaporated to dryness. The crude product was purified by ion-exchange

chromatography on DEAE Sephadex A-25, using a gradient of triethylammonium hydrogencarbonate buffers [0.1 ⟶ 1 mol dm^{-3}], pH 8.0, and was isolated as the triethylammonium salt **3** (34 μmol, determined by quantitative phosphate analysis); *m/z* (FAB; +ve) 423 $(M + H)^+$, 524 $(M + Et_3N + H)^+$, 625 $(M + 2Et_3N + H)^+$, 726 $(M + 3Et_3N + H)$; $\delta_H(D_2O$; 300 MHz) 3.67 (1 H, t, *J* 9, 6-H), 3.86 (1 H, ddd, *J* 13.06, 9 and 7.9, 3-H), 4.09 [2 H, 2 × ddd (overlapping), 4- and 5-H], 4.24 (1 H, ddt, *J* 13.06, 8.8 and 9, 1-H), and 4.44 (1 H, dt, *J* 51.19 and 9, 2-H); $\delta_P(D_2O$; 121.5 MHz) −0.089 (1 P, d, *J* 8.82, 1-OPO_3^{2-}), 0.767 (1 P, d, *J* 8.34, 5-OPO_3^{2-}) and 1.287 (1 P, d, *J* 7.97, 4-OPO_3^{2-}); $\delta_F(D_2O$; 282 MHz) −196.199 (1 F, dt, *J* 51.19 and 13.06, 2-F^{eq}).

(±)-1-O-*Allyl*-3,6-*di*-O-*benzyl*-4,5-O-*isopropylidine*-myo-2-*inosose* **16**.—A solution of compound **11** (3 g, 6.81 mmol) in dry DMSO (2.5 cm^3) was added dropwise *via* an addition funnel to a stirred solution of acetic anhydride (15 cm^3, 148 mmol) in dry DMSO (20 cm^3) under nitrogen at room temperature. After 16 h, TLC [ether–light petroleum (1:1)] showed complete conversion of starting material (R_f 0.36) into a product (R_f 0.47). The reaction mixture was added dropwise to stirred, aq. sodium hydrogencarbonate (50 g in 250 cm^3) during 1 h and the mixture was left for a further 2 h. The precipitated product was filtered off and washed well with water to give compound **16** as a solid (2.81 g, 94%), m.p. 123–125 °C (from ethyl acetate–light petroleum) (lit.,[35] 123–125 °C); ν_{max}/cm^{-1} 1740 (C=O) (Found: MH^+, 439.2121. Calc. for $C_{26}H_{31}O_6$: *m/z* 439.2121); *m/z* 439 (MH^+), 381 [$(M - OAllyl)^+$, 22%], 291 (30), 131 (15), 108 (53) and 91 (Bn^+, 100); $\delta_H(CDCl_3$; 300 MHz) 1.47 and 1.52 (6 H, 2 × s, CMe_2), 3.63 (1 H, dd, *J* 10.5 and 9, CH), 3.73 (1 H, *J* 9, CH), 3.94 (1 H, d, *J* 9, 3-H), 3.95 (1 H, t, *J* 9, CH), 4.05 (1 H, ddd, *J* 12, 6 and 1.5, C*H*HCH=CH_2), 4.20 (1 H, d, *J* 10.5, 1-H), 4.33 (1 H, ddd, *J* 12, 6 and 1.5, CH*H*CH=CH_2), 4.80 (4 H, m, 2 × CH_2Ph), 5.20 (1 H, ddt, *J* 10.5, 2.5 and 1.5, CH=C*H*H), 5.25 (1 H, ddt, *J* 16.5, 2.5 and 1.5, CH=CH*H*), 5.95 (1 H, ddt, *J* 16.5, 10.5 and 6, C*H*=CH_2) and 7.35 (10 H, m, CH_2*Ph*); $\delta_C([^2H_6]$Acetone; 75 MHz) 27.14 (q), 27.24 (q), 72.58 (t), 73.23 (t), 73.64 (t), 77.95 (d), 78.98 (d), 79.12 (d), 82.41 (d), 85.86 (d), 113.2 (s), 116.74 (t), 128.07 (d), 128.18 (d), 128.29 (d), 128.35 (d), 128.62 (d), 128.71 (d), 128.74 (d), 128.77 (d), 128.88 (d), 135.85 (d), 139.3 (d), 139.72 (s) and 203.14 (s).

(±)-1-O*Allyl*-3,6-*di*-*O*-*benzyl*-2-*deoxy*-2,2-*difluoro*-4,5-O-*isopropylidene*-myo-*inositol* **17**.—A solution of ketone **16** (1.6 g, 3.64 mmol) in dry dichloromethane (4 cm^3) was added dropwise to a stirred solution of DAST (1.92 cm^3, 14.5 mmol) in dry dichloromethane (2 cm^3) at room temperature under nitrogen; after 5 h, TLC [ether–light petroleum (1:1)] showed conversion of starting material (R_f 0.47) into a product (R_f 0.58). The reaction was quenched by cautious addition of saturated aq. sodium hydrogencarbonate. The dichloromethane solution was washed successively with saturated aq. sodium hydrogencarbonate (3 × 10 cm^3) and brine (2 × 10 cm^3), dried ($MgSO_4$), and evaporated. The crude product was chromatographed on silica gel [ethyl acetate–light petroleum (1:4)] to give *difluoride* **17** as an oil which solidified on storage (1.32 g, 79%), m.p. 88–88.5 °C (from ethyl acetate–hexane) (Found: MH^+, 461.2140. $C_{26}H_{31}F_2O_5$ requires MH^+, 461.2140); *m/z* 461 (MH^+, 2%), 419 (5), 369 (12), 181 (15), 131 (18), 107 (OBn^+, 6) and 91 (Bn^+, 100); $\delta_H(CDCl_3$; 300 MHz) 1.47 and 1.51 (6 H, 2 × s, CMe_2), 3.54 (2 H, m, 2 × CH), 3.74 (3 H, m, 3 × CH), 4.30 (2 H, m, CH_2CH=CH_2), 4.81 (4 H, m, 2 × CH_2Ph), 5.18 (1 H, ddt, *J* 10.5, 1.5 and 0.75, CH=C*H*H), 5.28 (1 H, ddt, *J* 16.5, 1.5 and 0.75, CH=CH*H*), 5.82 (1 H, ddt, *J* 16.5, 10.5 and 6, C*H*=CH_2) and 7.35 (10 H, m, 2 × CH_2*Ph*); $\delta_C(CDCl_3$; 75 MHz) 28.85 (q), 73.21 (t), 73.52 (t), 74.96 (t), 76.34, 76.56 and 76.99 (dt, C-1 or -3), 76.56 and 76.70 (dd, C-4 or -6), 77.41 and 77.53 (dd, C-6 or -4), 78.22 (d, C-5), 80.46, 80.73 and 81.00 (dt, C-1 or C-3), 112.87 (s), 117.3, 121.0 and 124.2 (t, C-2), 118.0 (t), 127.57 (d), 127.62 (d), 127.78 (d), 127.85 (d), 128.24 (d), 128.31 (d), 129.66 (d), 134.19 (d), 137.32 (s) and 138.14 (s); $\delta_F(CDCl_3$; 282 MHz) −123.8 (1 F, ddt, *J* 256, 4.8 and 16, 2-F^{eq}) and −111.5 (1 F, dt, *J* 256 and 4.8, 2-F^{eq}).

(±)-3,6-*Di*-O-*benzyl*-2-*deoxy*-2,2-*difluoro*-4,5-O-*isopropylidene*-1-O-(*prop*-1-*enyl*)-myo-*inositol* **18**.—Compound **17** (380 mg, 0.82 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (19 mg, 0.169 mmol) were heated to reflux temperature in ethanol–water (9:1; 10 cm^3). Wilkinson's catalyst (63.5 mg, 0.0686 mmol) was added down the condenser and washed into the reaction flask with the solvent mixture (4 cm^3). The reaction mixture was heated under reflux for 2 h, allowed to cool, poured into water, and the product was extracted into ether. The extract was washed with brine (2 × 15 cm^3), dried ($MgSO_4$), and evaporated. The crude material was purified by column chromatography on silica gel [ethyl acetate–light petroleum (1:4)] to give compound **18** (285 mg, 75% as a mixture of *E*- and *Z*-isomers [*E*:*Z*, 2:9], ν_{max}/cm^{-1} 1670 (OCH=CHMe); m.p. 109–111 °C (from ethyl acetate–hexane) (Found: MH^+, 461.2140. $C_{26}H_{31}F_2O_5$ requires MH^+, 461.2140); *m/z* 461 (MH^+), 369 [$(M - Bn)^+$, 4%], 107 (OBn^+, 10) and 91 (Bn^+, 100); $\delta_H(CDCl_3$; 300 MHz) 1.46 and 1.47 (6 H, 2 × s, CMe_2), 1.54 (3 H, dd, *J* 7.5 and 1.5, *E*-CH=CH*Me*), 1.65 (3 H, dd, *J* 6.0 and 1.5, *Z*-CH=CH*Me*), 3.56 (1 H, t, *J* 9, CH), 3.75 (4 H, m, 4 × CH), 4.50 (1 H, dq, *J* 6, *Z*-CH=C*H*Me), 4.80 (4 H, m, 2 × CH_2Ph), 5.13 (1 H, dq, *J* 12.75, 7.5, *E*-CH=C*H*Me), 6.05 (1 H, dq, *J* 6 and 1.5, *Z*-C*H*=CHMe), 6.15 (1 H, dq, *J* 12 and 1.5, *E*-C*H*=Me) and 7.35 (10 H, m, 2 × CH_2*Ph*); $\delta_C(CDCl_3$; 75 MHz) 8.82 (q, *Z*), 11.65 (q, *E*), 26.47 (q), 26.52 (q), 72.92 (t), 73.11 (t), 75.82 and 76.15 (dd, C-4 or -6), 76.28 and 76.44 (dd, C-6 or -4), 77.63 (d, C-5), 81.90, 82.17 and 82.52 (dt, C-1 or -3), 82.52, 82.79 and 83.06 (dt, C-3 or -1), 102.19 (d, *Z*), 102.64 (d, *E*), 112.67 (s), 116.49, 119.88 and 123.27 (t, C-2), 127.29 (d), 127.40 (d), 127.50 (d), 127.55 (d), 127.90 (d), 127.99 (d), 136.85 (s), 137.53 (s), 145.96 (d, *Z*) and 146.85 (d, *E*); $\delta_F(CDCl_3$; 282 MHz) −124.25 (1 F, ddt, *J* 254.16, 3.53 and 14.12, 2-F^{ax} (*Z*)], −123.9 (1 F, ddt, *J* 254.16, 3.53 and 14.12, 2-F^{ax} (*E*)], −112.4 (1 F, dt, *J* 254.16 and 3.54, 2-F^{eq} (*Z*)] and −111.0 [1 F, dt, *J* 254.16 and 3.54, 2-F^{eq} (*E*)].

(±)-3,6-*Di*-O-*benzyl*-2-*deoxy*-2,2-*difluoro*-myo-*inositol* **19ab**.—Compound **18** (200 mg, 0.43 mmol) was heated under reflux in 1 mol dm^{-3} hydrochloric acid–methanol (1:5; 10 cm^3) for 30 min. An excess of sodium hydrogencarbonate was added to the cooled reaction mixture and the solvents were evaporated off. The product was extracted from the residue with ethyl acetate and recrystallised from ethyl acetate–light petroleum to give *compound* **19ab** (142 mg, 86%), m.p. 194–195 °C (from ethyl acetate–light petroleum) (Found: C, 62.8; H, 5.8. $C_{20}H_{22}F_2O_5$ requires C, 63.15; H, 5.83%) [Found: $(M + NH_4)^+$, 398.1779. $C_{20}H_{26}F_2NO_5$ requires $(M + NH_4)^+$, 398.1779]; 289 [$(M - Bn)^+$, 28%], 107 (OBn^+, 40) and 91 (Bn^+, 100); $\delta_H([^2H_6]$-Acetone; 300 MHz) 3.40 (1 H, m, CH), 3.57 (2 H, m, 2 × CH), 3.69 (1 H, ddd, *J* 22.1, 10.5 and 3.6, C-H), 3.91 [1 H, dddd, *J* 22.1, 9, 3.6 and 6, (D_2O shake gives ddd, *J* 22.1, 9 and 3.6) 1-H], 4.45 (1 H, br s, exch. D_2O, COH), 4.66 (1 H, br s, exch. D_2O, OH), 4.90 (4 H, m, 2 × CH_2Ph), 4.95 (1 H, d, *J* 6, 1-OH) and 7.20–7.50 (10 H, m, 2 × CH_2*Ph*); $\delta_C([^2H_6]$Acetone; 75 MHz) 72.54, 72.80 and 73.06 (dt, C-1 or -3), 73.87 and 74.00 (dd, C-4 or -6), 74.82 (d, C-5), 75.45 (t), 75.74 (t), 79.90, 80.14 and 80.38 (dt, C-3 or -1), 82.14 and 82.26 (dd, C-6 or -4), 117.9, 121.0 and 124.4 (t, C-2), 127.9 (d), 128.17 (d), 128.43 (d), 128.72 (d), 128.83 (d), 139.50 (s) and 140.27 (s); $\delta_F([^2H_6]$Acetone; 282 MHz) −129.24 (1 F, dt, *J* 248.17 and 22.1, 2-F^{ax}) and −114.71 (1 F, dt, *J* 248.17 and 3.6, 2-F^{eq}).

2-*Deoxy*-2,2-*difluoro*-myo-*inositol* **20**.—Triol **19** (40 mg, 0.01 mmol), ethanol (5 cm^3), acetic acid (0.5 cm^3) and an excess of Pd on charcoal (10%) were shaken vigorously with hydrogen at 50 psi for 3 days. The Pd on charcoal was removed by filtration through Celite and washed with ethanol and water. The filtrate was evaporated to give crude compound **20** (15 mg, 71%), which was purified by recrystallisation from ethanol, m.p. 237–239 °C [Found: $(M + NH_4)^+$, 218.084. $C_6H_{14}F_2NO_5$ requires $(M + NH_4)^+$, 218.084]; $\delta_H(D_2O$; 300 MHz) 3.45 (3 H, m, 3 × CH), 3.78 (2 H, ddd, *J* 21.3, 9.0 and 4.2, 1- and 3-H); $\delta_F(D_2O$; 282 MHz) −115.38 (1 F, dt, *J* 244.8 and 4.2, 2-F^{eq}) and −130.28 (1 F, dt, *J* 244.8 and 21.3, 2-F^{ax}).

(±)-2-*Deoxy*-2,2-*difluoro*-myo-*inositol* 1,4,5-*Trisphosphate* **4**.—A mixture of triol **19** (60.9 mg, 160 μmol), tetrazole (144.8 mg, 2.06 mmol) and bis-(2-cyanoethyl)-(*N*,*N*-diisopropylamino)phosphine (500.4 mg, 1.84 mmol) was stirred at room temperature in dry dichloromethane (2 cm^3) for 1 h, after which time ^{31}P NMR spectroscopy showed the appearance of a signal at δ_P 141.8. The phosphite was oxidised by addition of *t*-butyl hydroperoxide [1 cm^3 (70% soln. in water)] at −78 °C. The reaction mixture was allowed to warm to room temperature. ^{31}P NMR spectroscopy showed complete conversion of the trisphosphite (δ_P 141.8) into the phosphate triester **21** (δ_P −2.2, −2.6, −2.9).

The reaction mixture was evaporated to dryness under reduced pressure. The crude product was partially purified by column chromatography on silica gel [dichloromethane–methanol (20:1)] to give the tris-triester.

Ammonia was condensed into a 3-neck flask at −78 °C and an excess of sodium was added. The dry liquid ammonia (40 cm^3) was distilled into a second 3-neck flask and kept at −78 °C. Sodium was added until the solution remained blue. The phosphate triester was added as a solution in dry 1,4-dioxane (4 cm^3). The reaction mixture was stirred for 15 min and then evaporated in a stream of nitrogen, and the crude product was taken up in water. The aq. solution was treated with H^+-Dowex until the solution became slightly acidic (universal indicator paper), and the Dowex was removed by filtration and washed well with water. The filtrate was made basic by the addition of triethylamine and evaporated to dryness. The crude product was purified by ion-exchange chromatography on DEAE Sephadex A-25 using a gradient of triethylammonium hydrogencarbonate buffers [0.1 ⟶ 1 mol dm^3], pH 8.0, and was isolated as the triethylammonium salt **4** (8.26 μmol, determined by quantitative phosphate analysis), *m*/*z* (FAB; +ve) 542 $(M + Et_3N + H)^+$ and 643 $(M + 2Et_3N + H)^+$; $\delta_H(D_2O$; 300 MHz) 4.03 (1 H, ddd, *J* 21.18, 9 and 3.6, 3-H), 4.14 (3 H, m, 3 × CH), 4.36 [1 H, ddt (overlapping), *J* 21.18, 9 and 3.6, 1-H]; $\delta_F(D_2O$; 282 MHz) −114.25 (1 F, dt, *J* 247.1 and 3.6, 2-F^{eq}) −128.65 (1 F, dt, *J* 247.1 and 21.18, 2-F^{ax}); $\delta_P(D_2O$; 121.5 MHz) 1.5 (1 P, d, *J* 9, 1-OPO_3^{2-}), 2.0 (1 P, d, *J* 8.4, C-OPO_3^{2-}) and 3.2 (1 P, d, *J* 8.21, C-OPO_3^{2-}).

(±)-3,6-*Di*-O-*benzyl*-2-*deoxy*-2,2-*difluoro*-4,5-O-*isopropylidene*-myo-*inositol* **22ab**.—Triol **19** (280 mg, 0.73 mmol), 2,2-dimethoxypropane (3.8 cm^3, 30 mmol), PTSA (38 mg) and dry acetone (15 cm^3) were stirred at room temperature under nitrogen for 2 h. Triethylamine (0.5 cm^3) and sodium hydrogencarbonate (280 mg) were added to the reaction mixture and the solvents were evaporated under reduced pressure. The product was extracted from the residue with dichloromethane and purified by flash column chromatography on silica gel [ethyl acetate–light petroleum (1:1)] to give *compound* **22** (230 mg, 75%), m.p. 153–155 °C (from ethyl acetate–hexane) (Found: MH^+, 421.1827. $C_{23}H_{27}F_2O_5$ requires MH^+, 421.1827); 421 (MH^+), 107 (OBn^+, 5%) and 91 (Bn^+, 100); $\delta_H(CDCl_3$; 300 MHz) 1.46 and 1.47 (6 H, 2 × s, CMe_2), 2.79 (1 H, d, *J* 4.5, 1-OH), 3.46 (1 H, t, *J* 9, CH), 3.44 [2 H, 2 × t (overlapping), *J* 9, 2 × CH], 3.72 (3 H, m, 3 × CH), 4.80 (4 H, m, 2 × CH_2Ph); $\delta_C(CDCl_3$; 75 MHz) 26.79 (q), 26.84 (q), 73.12 (t), 73.25 (t), 73.68, 73.96 and 76.24 (dt, C-1 or -3), 76.09, 76.32, 76.36 and 76.59 (ddd, C-3 or -1), 76.79 and 76.93 (dd, C-4 or -6), 77.03 and 77.14 (dd, C-6 or -4), 78.15 (d, C-5), 112.99 (s), 116.85, 120.22, 123.75 (t, C-2), 127.83 (d), 127.89 (d), 127.93 (d), 128.32 (d), 128.40 (d), 137.24 (s) and 137.78 (s); $\delta_F(CDCl_3$; 282 MHz) −113.67 (1 F, dt, *J* 254 and 4.4, 2-F^{eq}) and −126.93 (1 F, dm, *J* 254, 2-F^{ax}).

(−)-*Camphanate of* D- *and* L-3,6-*Di*-O-*benzyl*-2-*deoxy*-2,2-*difluoro*-4,5-O-*isopropylidene*-myo-*inositol*, **23** *and* **24**.—(*S*)-(−)-Camphanyl chloride (237 mg, 1.095 mmol) was added to a solution of racemic alcohol **22** (230 mg, 0.54 mmol) in dry pyridine (3 cm^3) and the solution was kept at room temperature overnight. The reaction mixture was diluted with water and products were extracted into ether. The extract was washed successively with dil. hydrochloric acid (2 × 10 cm^3) and saturated aq. potassium chloride (2 × 10 cm^3), dried (Na_2SO_4), and evaporated to give crude esters **23** and **24** (302 mg, 92%). The diastereoisomers were separated by flash chromatography on silica gel (100%; CH_2Cl_2) to give *ester* **23** (100 mg, 30%), m.p. 140–140.5 °C; $[\alpha]_D^{25}$ +32.02° (*c* 0.19, $CHCl_3$); R_f 0.19 (CH_2Cl_2); ν_{max}/cm^{-1} 1775 (C=O) (Found: MH^+, 601.2613. $C_{33}H_{39}F_2O_8$ requires MH^+, 601.2613); $\delta_H(CDCl_3$; 300 MHz) 0.92 (3 H, s, Me), 1.03 (3 H, s, Me), 1.09 (3 H, s, Me), 1.48 and 1.49 (6 H, 2 × s, CMe_2), 1.67 (1 H, ddd, camph.), 1.92 (2 H, m, camph.), 2.31 (1 H, ddd, camph.), 3.65 (1 H, t, *J* 9, CH), 3.75 (1 H, dt, *J* 9 and 3.75, 3-H), 3.86 (2 H, m, 2 × CH), 4.55–4.9 (4 H, m, 2 × CH_2Ph), 5.36 (1 H, ddd, *J* 18.58, 3.75 and 9, 1-H) and 7.20–7.45 (10 H, m, 2 × CH_2Ph); $\delta_C(CDCl_3$; 75 MHz) 9.61 (q), 16.29 (q), 16.51 (q), 26.76 (q), 26.79 (q), 29.02 (t), 30.56 (t), 54.36 (s), 54.71 (s), 72.28, 72.65 and 72.83 (dt, C-1 or -3), 72.56 (t), 73.43 (t), 74.64 and 74.75 (dd, C-4 or -6), 75.79, 76.02 and 76.29 (dt, C-3 or 1), 76.70 and 76.84 (dd, C-6 or -4), 78.25 (d, C-5), 90.87 (s), 113.43 (s), 115.9, 119.2, 122.8 (t, C-2), 127.72 (d), 127.93 (d), 127.98 (d), 128.31 (d), 128.38 (d), 136.86 (s), 137.38 (s), 165.91 (s) and 177.56 (s); $\delta_F(CDCl_3$; 282 MHz) −112.86 (1 F, dt, *J* 252 and 3.75, 2-F^{eq}) and −121.72 (1 F, ddt, *J* 252, 18.58 and 3.75, 2-F^{ax}); and *ester* **24** (121 mg, 32%), m.p. 141–141.5 °C; $[\alpha]_D^{25}$ −20.52° (*c* 0.19, $CHCl_3$); R_f 0.29 (CH_2Cl_2); ν_{max}/cm^{-1} 1775 (C=O) (Found: MH^+, 601.2613); *m*/*z* 601 (MH^+), 509 [$(M - Bn)^+$, 5%], 205 (6), 181 (Camph.$^+$, 5) and 91 (Bn^+, 100); $\delta_H(CDCl_3$; 300 MHz) 0.892 (3 H, s, Me), 0.98 (3 H, s, Me), 1.09 (3 H, s, Me), 1.47 and 1.48 (6 H, 2 × s, CMe_2), 1.65 (1 H, ddd, camph.), 1.91 (2 H, m, camph.), 2.44 (1 H, ddd, camph.), 3.63 (1 H, t, *J* 9, CH), 3.78 (1 H, dt, *J* 9 and 3.75, 3-H), 3.90 (2 H, m, 2 × CH), 4.60–4.95 (4 H, m, 2 × CH_2Ph), 5.35 (1 H, ddd, *J* 18.58, 9 and 3.75, 1-H), 7.20–7.45 (10 H, m, 2 × CH_2Ph); $\delta_C(CDCl_3$; 75 MHz) 9.69 (q), 16.36 (q), 16.51 (q), 26.73 (q), 26.79 (q), 28.81 (t), 30.53 (t), 54.48 (s), 54.82 (s), 72.61, 72.83 and 73.38 (dt, C-1 or -3), 72.82 (t), 73.38 (t), 74.97 and 75.09 (dd, C-4 or -6), 75.85, 76.35 and 76.62 (dt, C-3 or -1), 76.71 and 76.85 (dd, C-6 or -4), 78.16 (d, C-5), 90.88 (s), 113.3 (s), 115.81, 119.17 and 122.58 (t, C-2), 127.38 (d), 127.62 (d), 127.90 (d), 127.93 (d), 128.23 (d), 128.35 (d), 136.91 (s), 137.44 (s), 166.25 (s), and 177.82 (s); $\delta_F(CDCl_3$; 282 MHz) −112.91 (1 F, dt, *J* 252.2 and 3.75, 2-F^{eq}) and −122.35 (1 F, ddt, *J* 252.2, 18.58 and 3.75, 2-F^{ax}). The absolute configuration of **23** was determined by single-crystal X-ray crystallography.

D-3,6-*Di*-O-*benzyl*-2-*deoxy*-2,2-*difluoro*-myo-*inositol* **19a**.—Camphanate **23** (100 mg, 0.16 mmol), sodium hydroxide (45 mg) and methanol (4 cm^3) were heated under reflux for 1 h, and the reaction mixture was cooled, neutralised with solid carbon dioxide, and evaporated. The residue was taken up in toluene

(2×10 cm^3) and the toluene was evaporated off. The product was extracted from the residue into dichloromethane and evaporated to give crude D-(**22a**) (73.2 mg, 97%), identical with racemic alcohol DL-**22ab** by TLC, which was used without further purification.

Alcohol **22a** (73.2 mg, 0.17 mmol) was heated under reflux in methanol–mol dm^{-3} HCl (9:1; 10 cm^3) for 30 min. The reaction mixture was allowed to cool, an excess of sodium hydrogencarbonate was added, and the solvents were evaporated off. The product was extracted into ethyl acetate and purified by flash chromatography on silica gel [ethyl acetate–light petroleum (1:1)] to give optically pure enantiomer **19a** (55.1 mg, 90%), m.p. 152–153 °C; $[\alpha]_D^{25}$ +10.79° (*c* 0.19, acetone). Mass spectra and NMR data were identical with those obtained for racemic triol **19**.

L-3,6-*Di*-O-*benzyl*-2-*deoxy*-2,2-*difluoro*-myo-*inositol* **19b**.—Similar reaction and work-up of Camphanate **24** (121 mg, 0.2 mmol), sodium hydroxide (50 mg) and methanol (5 cm^3) gave crude L-alcohol **22b** (83 mg, 98%), identical with racemic alcohol **22ab** by TLC, which was used without further purification.

Alcohol **22b** (83 mg, 0.19 mmol) was similarly hydrolysed, and the product was worked up as before to afford optically pure triol **19b** (47 mg, 62%), m.p. 152–153 °C; $[\alpha]_D^{25}$ −11.19° (*c* 0.192, acetone). Mass spectra and NMR data were identical to those obtained for racemic triol **19ab**.

D-2-*Deoxy*-2,2-*difluoro*-myo-*inositol* 1,4,5-*Trisphosphate* **4a**.—A mixture of triol **19a** (55.1 mg, 145 μmol), tetrazole (101 mg, 1.43 mmol) and bis-(2-cyanoethyl)-(*N*,*N*-diisopropylamino)phosphine (236 mg, 0.87 mmol) was stirred at room temperature in dry dichloromethane (2 cm^3) for 1 h, after which time ^{31}P NMR spectroscopy showed the appearance of a signal at δ_P 141.58. The phosphite was oxidised at −78 °C by addition of *t*-butyl hydroperoxide [1 cm^3 (70% soln. in water)]. The reaction mixture was allowed to warm to room temperature. ^{31}P NMR spectroscopy showed complete conversion of the trisphosphite (δ_P 141.58) into the phosphate triester (δ_P −2.22, −2.69, −2.96). The reaction mixture was evaporated under reduced pressure. The crude product was partially purified by column chromatography on silica gel [dichloromethane–methanol (20:1)] to give the trisphosphate.

Ammonia was condensed into a 3-neck flask at −78 °C and an excess of sodium was added. The dry liquid ammonia (40 cm^3) was distilled into a second 3-neck flask and kept at −78 °C. Sodium was added until the solution remained blue. The phosphate triester was added as a solution in dry 1,4-dioxane (3 cm^3). The reaction mixture was stirred for 15 min and then quenched by addition of ethanol. The ammonia was evaporated off in a stream of nitrogen and the crude product was taken up in water. The aq. solution was treated with H^+-Dowex until the solution became slightly acidic (universal indicator paper), and the Dowex was removed by filtration and washed well with water. The filtrate was made basic by the addition of triethylamine and evaporated to dryness. The crude product was purified by ion-exchange chromatography on DEAE Sephadex A-25 by using a gradient of triethylammonium hydrogencarbonate buffers (0.1 ⟶ 1 mol dm^{-3}), pH 8.0, and isolated as the triethylammonium salt **4a** (6.5 μmol), $[\alpha]_D^{25}$ −23.3° (*c* 0.057, water). Spectral data as for racemic **4**.

L-2-*Deoxy*-2,2-*difluoro*-myo-*inositol* 1,4,5-*Trisphosphate* **4b**.—Triol **19b** (47 mg, 123 μmol) was phosphorylated and deprotected as described above for the D-isomer to give compound **4b** (2.2 μmol), $[\alpha]_D^{25}$ +24.0° (*c* 0.019, water). Spectral data as for racemic **4**.

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